Attorney Docket No. AVIR-0335

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Application of: William D Huse *et al.*
Serial No.: 09/434,870 Group No.: 1642
Filed: 11/04/99 Examiner: L. Helms
Entitled: **Methods of Optimizing Antibody Variable Region Binding Affinity**

# SECOND DECLARATION OF DR. JEFFRY D. WATKINS PURSUANT TO 37 C.F.R. § 1.132

Assistant Commissioner for Patents
Washington, D.C. 20231

#28 KO 3-6-03

**CERTIFICATE OF MAILING UNDER 37 C.F.R. § 1.8(a)(1)(i)(A)**

I hereby certify that this correspondence (along with any referred to as being attached or enclosed) is, on the date shown below, being deposited with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231.

Dated: January 29, 2003 By: Traci E. Light

I, Dr. Jeffry D. Watkins, under penalty of perjury state that:

1. I am a joint inventor of the subject matter claimed in the above-captioned United States Patent Application. I am presently employed as the Chief Scientific Officer at Applied Molecular Evolution, Inc. (formerly Ixsys, Inc.), the Assignee of the above-captioned United States Patent Application. I previously submitted a declaration during this prosecution.

2. I have read the office action mailed 10/29/02 wherein the Examiner argues that the pending claims are obvious in view of Deng et al. (along with some other references). In particular, I noted the Examiner's citation to page 13 (lines 2-16) of the Deng et al. reference and the Examiner's statement (on page 3 of the office action) that "Deng et al teach a method of humanization using randomization of exposed residues resulting in a resurfacing of the antibody and it is obvious that resurfacing would result in randomization of both framework and CDR as both of these are surface exposed residues."

3. I noted the "resurfacing" text on page 13 to which the Examiner refers. Deng et al. speaks of randomizing "exposed residues of the murine antibodies." This is not a selection of *which* residues to change based on two reference sequences "that differ at the corresponding position" as presently claimed. This is a selection based on what residues are "exposed" and thus is a completely different approach from the one presently claimed. Thus, even if both framework and CDR residues are taught to be changed in the Deng et al. resurfacing approach (something which the Examiner assumes without any explicit support in the text), the changes are being made using different rules than specifically required in the presently drafted claims.

4. While Deng et al. teaches a method of simultaneously making changes in more than one place in a gene, Deng et al. do not teach the grafting and reacquisition of binding in a single step as taught in the specification. For example, the present specification notes (at page 17, lines 19-25) not merely simultaneous changes, but simultaneous *procedures*:

> "[In prior art approaches]. . . once the CDR-grafted antibody, or variable region binding fragment is made, it requires subsequent rounds of molecular engineering to reacquire binding affinity comparable to the donor antibody. The present invention combines these steps such that CDR grafting and binding reacquisition occur in a single simultaneous procedure."

At no point in Deng et al. is it taught that these two *procedures* are to be performed in one step. Rather, Deng et al. teaches either i) optimization (or "maturation") of an existing antibody (e.g. by simultaneous changes in three CDRs - see Example 1 and Figure 2), or ii) humanization by simultaneous multiple changes in frameworks (Example 3).

5. I have read the Deng et al. reference, including the page 13 text to which the Examiner refers. The text on page 12 provides the context for some of the sentences on page 13 of Deng et al. At lines 20-26 of page 12, Deng et al. speaks of *maturation* of antibody wherein the six CDRs are randomized. The text at lines 28-37 of page 12 deals with *humanization* where "selected residues in human frameworks are randomized."

6. On page 13, Deng et al. summarizes by saying "not only can the CDRs be randomized but also the frameworks." As one skilled in the art, I read this sentence to simply be summarizing that the Deng et al. approach can be used for either of the two applications discussed prior to the sentence, namely the maturation discussed on page 12 or the humanization discussed on pages 12-13. Thus, I do not read the sentence as teaching simultaneous changes in both the CDRs and the frameworks. Moreover, *even if one were to read the sentence as teaching simultaneous changes in CDRs and frameworks,* there is no teaching of simultaneous grafting and reacquisition. Thus, the Examiner cannot equate simultaneous changes with the simultaneous performance of grafting and reacquisition.

7. My interpretation of pages 12 and 13 of Deng et al. is justified based on the complete text of the specification and the examples. At no point does Deng et al. provide either a teaching in the specification or an example where the two procedures of grafting and reacquisition take place in a single step.

8. It is somewhat counterintuitive to perform grafting and reacquisition in one step. Most prior art methods first evaluate the degree to which grafting has caused the loss of affinity - *before* attempting to reacquire it. The presently claimed method, however, assumes that grafting alone will result in lower affinity.

9. The undersigned declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, and that such willful false statements may jeopardize the validity of the application or any patent issuing therefrom.

Dated: 1-27-07

Jeffry Watkins, Ph.D.